AK1

Consommation et Corporations Canada
Consumer and Corporate Affairs Canada
Bureau des brevets
Patent Office
Ottawa, Canada
K1A 0C9

(21) (A1) 2,020,018
(22) 1990/06/27
(43) 1991/12/28
(52) 167-220
C.R. CL. 167-223
167-231
167-268

5,024,5/00

(51) INTL.CL.[5] A61K-31/52; A61K-31/495; A61K-31/445; A61K-31/165

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Method and Composition for Treating the Migraine Complex

(72) Simmons, Don L. - Canada ;

(73) Same as inventor

(57) 10 Claims

ABSTRACT OF THE DISCLOSURE

Oral compositions comprising in combination an analgesic, an antinauseant and one or more antacid ingredients have been shown to be effective in the treatment of acute migraine attacks.

The present invention relates to oral compositions comprising in combination, an analgesic, an antinauseant and one or more antacid ingredients for the treatment of acute migraine attacks.

More specifically the present invention is an oral tablet medication containing as active ingredients the analgesic acetaminophen, the antinauseant dimenhydrinate, and the antacids, aluminum and magnesium hydroxides. Without limiting the scope of this disclosure, the relative amounts are acetaminophen 325 mg, dimenhydrinate 25 mg, aluminum hydroxide 100 mg and magnesium hydroxide 50 mg.

Migraine attacks affect about 20% of the population and the cause of this debilitating condition is still uncertain today. Migraines may be described as recurring attacks of headache, varying widely in intensity, frequency, and duration. The majority of migraine attacks are also associated with gastrointestinal symptoms which add considerably to the distress and inconvenience caused by the headache. The range of gastrointestinal symptoms in migraine varies from mild nausea to severe vomiting. In a prospective survey of 500 patients attending a specialist outpatient migraine clinic in 1966, Lance and Anthony in Archives of Neurology, volume 15, pages 356-361, found that 96% of patients experienced gastrointestinal symptoms during migraine. The majority of these subjects (93%) reported nausea with 75% of them also experience vomiting. Similarly, in a 1974 survey of 600 acute attacks of migraine, Wilkinson et al in Abstracts of the Sixth Migraine Symposium - Migraine Trust, London 1974 found that nausea occurred in 2/3 with vomiting

prevalent in nearly 1/4 of the attacks. It is obvious that vomiting will reduce the efficacy of orally administered drugs and it has been recently recognized that even if the ingested drugs are retained, they may not be absorbed at the normal rate and that this might be the reason for therapeutic failures seen in migraine patients. Volans in a November 1974 issue of British Medical Journal tested this hypothesis by performing a comparative salicylate absorption study of effervescent aspirin tablets in patients during migraine attacks. He found that the rate of salicylate absorption in migrainous patients was reduced relative to that found in non-migrainous volunteers and, in the same migraine patients when headache-free. This reduced rate of absorption is evidently caused by gastrointestinal stasis and corresponding reduced rate of gastric emptying. Nimmo and coworkers in a March 1974 issue of British Medical Journal have investigated the effects of drug-induced changes on gastric emptying and the corresponding absorption rate of acetaminophen - a drug in which absorption is dependent on the rate of gastric emptying. Propantheline delayed gastric emptying and markedly slowed the absorption of acetaminophen in subjects while the absorption was accelerated by metoclopramide, a drug which stimulates gastric emptying.

Various medications are available for treating migraine attacks. Gawel has reviewed the role of symptomatic and prophylactic drug therapy in a September 1986 issue of Revue Pharmaceutique Canadienne. The infrequent migraine episode is best treated symptomatically, and ergotamine, alone or in combination, is the mainstay of treatment. Unfortunately, 40%

of patients find that the side effects preclude its use. Ergotamine is usually combined with an antiemetic such as metoclopramide or domperidone to enhance the effectiveness. Acetylsalicylic acid and acetaminophen, again with an antiemetic (identity not disclosed), can be very effective. Other combination medications such as FIORINAL* (acetylsalicylic acid + caffeine + butalbital with and without codeine) and MERSYNDOL* (acetaminophen + codeine + doxylamine) can be extremely useful but care must be taken when prescribing medications containing sedatives and codeine since dependence may result. Some of the new nonsteroidal anti-inflammatory drugs (NSAID's) also possessing analgesic activity such as ibuprofen, naprosyn, ketoprofen, diflunisal, etc., although useful as prophylactic medication, can also be used symptomatically. Some patients respond well to these, while in others there is no effect. The aim of symptomatic therapy is to give enough medication early enough, before headache sets in. Prophylactic treatment has achieved some success with beta clockers (propranolol, nadolol, atenolol), tricyclic antidepressants (amitryptiline, nortryptiline), monoamine oxidase inhibitors (phenelzine, deprenyl) and calcium channel blockers (diltiazem, verapamil) but they all seem to have a limited period of efficacy and the side effects are numerous.

The two non-prescription analgesics most commonly ingested by patients at the onset of a migraine are acetaminophen and acetylsalicylic acid (ASA). Ibuprofen is also useful in treating migraines but there has been some recent adverse publicity concerning possible kidney problems associated with

*TM

overuse of this drug. Similarly, the gastrointestinal irritation and bleeding problems that arise in many patients following ASA ingestion has led the inventor to concentrate his efforts on the analgesic acetaminophen for the purpose of this disclosure. However, the fact that ASA and ibuprofen are used symptomatically in treating an acute condition does not exclude them for use as analgesics in this invention.

The principal object of the invention therefore, bearing in mind the foregoing comments, is to provide oral compositions designed for the relief of migraine attacks or, in other words, for the symptomatic relief of the headache and nausea characteristic of the migraine condition.

Another object of the invention is to provide novel compositions containing in combination effective proportions of an analgesic and an antinauseant together with one or more antacid ingredients, sufficient to provide relief of migraine headaches.

A further object of the invention is the provision of an effective method of alleviating the pain characteristic of the migraine complex, consisting in the administration of oral compositions including in admixture an analgesic and an antinauseant together with one or more antacid substances. As an anti-migraine formulation according to the invention we have prepared a fast disintegrating oral tablet containing the following active ingredients:

acetaminophen	325 mg
dimenhydrinate	25 mg
aluminum hydroxide	100 mg

magnesium hydroxide 50 mg

The dosage is one or two tablets immediately at the onset of an attack followed, if needed, by one or two tablets every four hours, not to exceed 8 tablets in a 24 hour period. It is believed that the combination of an analgesic, an antinauseant and one or more antacids does not exist and has never been prescribed for the treatment of migraine attacks. However, analgesics have been combined with antacids. For example, Whitehall's "Arthritis Pain Formula"* contains ASA 486 mg and aluminum hydroxide 20 mg and magnesium hydroxide 60 mg; Bristol-Myers "Arthritis Strength Bufferin"* has ASA 486 mg along with magnesium carbonate and aluminum glycinate; Rorer's "Ascriptin"* has ASA 325 mg, magnesium hydroxide 75 mg and aluminum hydroxide 75 mg; Glenbrook's "Vanquish Caplet"* contains ASA 227 mg, acetaminophen 184 mg, magnesium hydroxide 50 mg, aluminum hydroxide 25 mg and caffeine 33 mg. Acetaminophen 500 mg has also been combined with diphenhydramine citrate 38 mg by Bristol-Myers in their product "Excedrin P.M."* as an analgesic sleep aid. The latter formula would be similar to the present invention if antacids were also incorporated since dimenhydrinate is a complex of diphenhydramine and 8-chlorotheophylline in contrast to diphenhydramine and citric acid. The corresponding amounts of diphenhydramine are 13.58 and 21.68 mg, respectively. The indication for Excedrin P.M.* is treatment of mild headaches and sleeplessness.

Analgesics have also been combined with anti-emetics or antinauseants with and without codeine. For example, both ASA and acetaminophen have been combined with metoclopramide and are

*TM

commercially available in the United Kingdom. Bayer market the products "Migravess"* and "Migravess Forte"* which are presented as soluble scored tablets containing either ASA 325 mg or ASA 450 mg, and metoclopramide hydrdochloride 5 mg. Beecham market a product "Paramax"* which is available in both tablets and sachets and both contain acetaminophen 500 mg and metoclopramide hydrochloride 5 mg. These products were observed by Steiner and Rose to work reasonably well when administered to migraine patients attending the Princess Margaret Migraine Clinic in London, England. These authors reported their findings in a review article on problems encountered in the assessment of treatment of headache and migraine which appeared in the textbook, Headache, Publishers W. B. Saunders, 1988. For first-line acute therapy for migraine at the Clinic, these authors use simple analgesics such as ASA or acetaminophen, or one of several NSAID's, preferably in a soluble formulation, with metoclopramide to improve gastric emptying whether there is nausea or not. Parenteral metoclopramide was administered to overcome gastric stasis. Another product widely used in the United Kingdom for treating migraine is "Migraleve"* or "Migralift"* which is marketed by International Laboratories and contains the anti-emetic buclizine hydrochloride 6.25 mg, paracetamol or acetaminophen 500 mg and codeine phosphate 8 mg.

The ingredients disclosed in this invention have been commercially available as separate over-the-counter medications for many years and have been indicated for treating mild to moderate pain, motion sickness and accompanying nausea and vomiting, and various stomach disorders.

*TM

Prior to the introduction time of the systemic anti-ulcer-agents cimetidine and ranitidine, any gastric ulcer patient who simultaneously suffered from headaches and motion sickness obviously had cause to combine these various medications.

Samples of these tablets have been given to women who have suffered from classic or common migraine attacks for many years and who have been prescribed all of the known medications for treating this affliction. Without exception, the women have stated that this new tablet formulation is superior to other medications, particularly when taken at the onset of an attack.

The key to the success of these tablets appears to be the rapid disintegration features of the tablet along with the presence of the antacid components and their effect on gastrointestinal motor activity. Alkalinization of the gastric contents increases gastric motility through the action of gastrin and therefore would alleviate the gastric stasis that occurs with the onset of migraine attacks. The net effect of this enhanced gastric motility is a rapid and unimpeded delivery of acetaminophen and dimenhydrinate to the area of the small intestine for immediate dissolution, absorption, and distribution. These drugs are therefore biologically available for treating any pain or nausea that might develop during the migraine episode.

Other analgesics that may be used in this invention are acetylsalicylic acid, ibuprofen and other non-steroidal anti-inflammatory drugs (NSAID's) also possessing analgesic activity such as naproxen or its sodium salt, ketoprofen, diflunisal, etc., other anti-emetic or antinauseant drugs such as

metoclopramide, domperidone, buclizine, etc., and other antacids such as calcium carbonate, magnesium carbonate, aluminum hydroxide-magnesium carbonate co-dried gel, etc.

The oral composition may be a capsule or a direct compression or granulated tablet as exemplified below. Other tablet glidants, lubricants, disintegrating agents, fillers, etc., may be used in preparing the tablets and the following examples are given by way of illustration and not of limitation.

Example 1

A direct compression formulation for 10,000 tablets containing the following ingredients is prepared as described below:

Acetaminophen (direct compression grade, 90%)	3,620 gms
Dimenhydrinate	250 gms
Magnesium Hydroxide High Density Grade	500 gms
Aluminum Hydroxide Dried Gel High Density Grade	1,000 gms
Microcrystalline Cellulose (Avicel PH-102)	1,250 gms
Croscarmellose Sodium (Ac-Di-Sol)	80 gms
D&C Yellow #10 Lake (15%)	4 gms
Colloidal Silicon Dioxide (Aerosil 200)	25 gms
Magnesium Stearate	80 gms

Approximately one-half of the microcrystalline cellulose is intimately mixed with magnesium hydroxide, aluminum hydroxide dried gel and the direct compression grade acetaminophen. The remaining ingredients are intimately mixed separately and screened manually through a #40 stainless steel screen. The two portions are then mixed together and compressed using a suitable tablet press to a tablet weight of 683 mg.

Example 2

A granulation formulation for 10,000 tablets containing the following ingredients is prepared as described below:

Acetaminophen (direct compression grade, 90%)	3,620 gms
Dimenhydrinate	250 gms
Magnesium Hydroxide High Density Grade	500 gms
Aluminum Hydroxide Dried Gel High Density Grade	1,000 gms
Microcrystalline Cellulose (Avicel PH-102)	400 gms
Pregelatinized Starch (Starch 1500)	460 gms
Purified Water Q S	
Croscarmellose Sodium (Ac-Di-Sol)	40 gms
D&C Yellow #10 Lake (15%)	4 gms
Colloidal Silicon DIoxide (Aerosil 200)	20 gms
Magnesium Stearate	60 gms

The same general procedure used in Example 1 was followed here except the antacid components were granulated using the pregelatinized starch and purified water and the resulting wet granules spread on trays and dried in a suitable oven. The dried granules were sized and mixed with the remaining powders and compressed as before.

Single tablet formulations could be as follows:

Example 3

	Ingredients	I mg/tab.	II mg/tab.
1.	Acetaminophen, USP	325	325
2.	Dimenhydrinate, USP	25	25
3.	Magnesium Hydroxide, USP	50	50
4.	Aluminum Hydroxide Dried Gel, USP	100	100

5.	Microcrystalline cellulose, NF	125	40
6.	Pregelatinized Starch, NF		46
7.	Croscarmellose Sodium, NF	8	4
8.	D&C Yellow #10 Lake	0.4	0.4
9.	Colloidal Silicon Dioxide, NF	2.5	2.0
10.	Magnesium Stearate, NF	8	6

An alternate formulation II, in which the antacid components are granulated with starch paste, was prepared in the event problems might be encountered in high-speed tablet presses with direct compression formula I.

The essential characteristics of the present invention will readily be understood and appreciated by persons skilled in the art, and such persons will without difficulty be able to devise modifications, within the scope of the disclosure, for the purpose of adapting the invention to various conditions and circumstances, and will at all times be aware that any such modifications fall within the scope of the appended claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. An oral composition for the treatment of acute migraine attacks comprising in combination an analgesic, an antinauseant and at least one antacid ingredient.

2. A composition according to claim 1, the analgesic being acataminophen, or a non-steroidal anti-inflammatory drug (NSAID) also possessing analgesic properties and selected from the group: acetylsalicylic acid, ibuprofen, naproxen or its sodium salt, ketoprofen, diflunisal; the antinauseant being selected from the group: dimenhydrinate, metoclopramide hydrochloride, domperidone, buclizine hydrochloride; the antacid ingredient being selected from the group: magnesium hydroxide, aluminum hydroxide, calcium carbonate, magnesium carbonate and aluminum hydroxide/magnesium carbonate co-dried gel.

3. A composition according to claim 2 comprising the following additional ingredients: glidants, lubricants, disintegrating agents, fillers and pigmenting materials.

4. A composition according to claims 1 and 2 comprising acetaminophen, dimenhydrinate, magnesium hydroxide and aluminum hydroxide.

5. A composition according to claim 3 containing the following ingredients:

Acetaminophen, USP	325	mg
Dimenhydrinate, USP	25	mg
Magnesium Hydroxide, USP	50	mg
Aluminum Hydroxide, USP	100	mg
Microcrystalline Cellulose, NF	125	mg
Croscarmellose Sodium, NF	8	mg

D&C Yellow #10 Lake (15%)	0.4 mg
Colloidal Silica, NF	2.5 mg
Magnesium Stearate, NF	8 mg

6. A composition according to claim 3 containing the following ingredients:

Acetaminophen, USP	325 mg
Dimenhydrinate, USP	25 mg
Magnesium Hydroxide, USP	50 mg
Aluminum Hydroxide, USP	100 mg
Microcrystalline Cellulose, NF	40 mg
Pregelatinized Starch, NF	46 mg
Croscarmellose Sodium, NF	4 mg
D&C Yellow #10 Lake (15%)	0.4 mg
Colloidal Silica, NF	2 mg
Magnesium Stearate, NF	6 mg

7. The method of alleviating the pain characteristic of the migraine complex comprising administering an oral composition including in admixture an analgesic, an antinauseant and at least one antacid ingredient.

8. The method of alleviating the pain characteristic of the migraine complex according to claim 7, the analgesic being acetaminophen, or a non-steroidal anti-inflammatory drug (NSAID) also possessing analgesic properties and selected from the group: acetylsalicylic acid, ibuprofen, naproxen or its sodium salt, ketoprofen, diflunisal; the antinauseant being selected from the group: dimenhydrinate, metoclopramide hydrochloride, domperidone, buclizine hydrochloride; the antacid ingredient being selected from the group: magnesium hydroxide, aluminum hydroxide, calcium carbonate, magnesium carbonate, and aluminum hydroxide/magnesium carbonate co-dried gel.

9. The method according to claim 8 of alleviating the pain characteristic of the migraine complex comprising administering the following composition:

Acetaminophen, USP	325	mg
Dimenhydrinate, USP	25	mg
Magnesium Hydroxide, USP	50	mg
Aluminum Hydroxide Dried Gel, USP	100	mg
Microcrystalline cellulose, NF	125	mg
Croscarmellose Sodium, NF	8	mg
D&C Yellow #10 Lake (15%)	0.4	mg
Colloidal Silica, NF	2.5	mg
Magnesium Stearate, NF	8	mg

10. The method according to claim 8 of alleviating the pain characteristic of the migraine complex comprising administering the following composition:

Acetaminophen, USP	325	mg
Dimenhydrinate, USP	25	mg
Magnesium Hydroxide, USP	50	mg
Aluminum Hydroxide, USP	100	mg
Microcrystalline cellulose, NF	40	mg
Pregelatinized Starch, NF	46	mg
Croscarmellose Sodium, NF	4	mg
D&C Yellow #10 Lake (15%)	0.4	mg
Colloidal Silica, NF	2	mg
Magnesium Stearate, USP	6	mg

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente